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ТРУДНОСТИ ДИАГНОСТИКИ ПАЦИЕНТА С ЛИХОРАДКОЙ НЕЯСНОГО ГЕНЕЗА

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Difficulties in Diagnosing a Patient with Fever of Unknown Origin

Резюме

Лихорадка неясного генеза представляет собой сложный для дифференциальной диагностики синдром. При отсутствии ключевого признака, который мог бы указать на причину состояния дальнейший диагностический поиск становится затруднительным. Осложняет диагностику многообразие причин и отсутствие единого алгоритма обследования. В представленном клиническом случае описывается пациентка 53 лет, с длительной лихорадкой более 1.5 месяцев, болевым синдромом в области лица. При амбулаторном наблюдении причина выяснена не была. На стационарном этапе проведено комплексное обследование по всем классам причин. Выявленные изменения щитовидной железы и наличие тиреотоксикоза позволили поставить диагноз подострого тиреоидита. Согласно данным литературы, подострый тиреоидит является одной из редких причин лихорадки неясного генеза. Назначение глюкокортикостероидов позволило достигнуть полного регресса клинических симптомов к 4 суткам. Через 5 месяцев достигнут субклинический гипотиреоз. Нозологический подход и междисциплинарное взаимодействие способствовали верной тактике и благоприятному исходу заболевания.

Ключевые слова: *лихорадка неясного генеза, подострый тиреоидит*

Конфликт интересов

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Abstract

Fever of unknown origin is a difficult syndrome for differential diagnosis. Absence of a key feature, variety of causes and the lack of single examination algorithm makes difficult further diagnosis. The presented clinical case describes a 53-year-old patient with a prolonged fever of more than 1.5 months, pain syndrome in the facial area. During outpatient monitoring, the cause was not clarified. At the inpatient stage, a comprehensive examination was conducted for all classes of causes. The revealed changes in the thyroid gland and thyrotoxicosis made it possible to diagnose subacute thyroiditis. According to the literature, subacute thyroiditis is one of the rare causes of fever of unknown origin. Prescription of glucocorticosteroid made it possible to achieve complete regression of clinical symptoms in 4 days. After 5 months, subclinical hypothyroidism was achieved. The nosological approach and multidisciplinary interaction contributed to the correct tactics and a favorable outcome of the disease.

Key words: *fever of unknown origin, subacute thyroiditis*

Conflict of interests

Co-author of the article Adasheva T.V. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Adasheva T.V. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

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Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «Difficulties in Diagnosing a Patient with Fever of Unknown Origin» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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FUO — fever of unknown origin, GCS — glucocorticosteroids, CRP — C-reactive protein, ESD — erythrocyte sedimentation rate, CT — computer tomography, TTH — thyrotropic hormone, free T3 — free triiodothyronine, free T4 — free thyroxine, GCA — giant cell arteritis

"The true knowledge is the knowledge of causes"
Galileo Galilei

For the first time, fever of unknown origin (FUO) was mentioned in 1930 in a report by a US hospital. Scientists described a follow-up of 173 patients starting from 1913, who were discharged with the diagnosis "fever of unknown origin".

In 1961, R.G. Petersdorf and P.B. Beeson proposed the first official definition of fever of unknown origin: "A fever of over 100.9 F (38.3 ˚C) in some cases, persisting without a diagnosis for three weeks, despite one week of inpatient examinations" [1].

30 years later, Durack D.T. and Street A.C. modified this definition: undefined diagnosis after three visits to the doctor or a 3-day inpatient examination [2].

It is important to note that the body temperature can vary by 0.7 ˚C depending on the place of measurement. In Europe and the USA, temperature is usually measured in the oral cavity or rectum, while in Russia, the most common is axillary crease. Therefore, criteria of FUO can be temperature less than 38.3 ˚C.

The aetiology of FUO includes five groups of the most common causes: infections (40 %), tumours (20 %), inflammatory connective tissue diseases (20 %), returned traveller diseases, and other (10 %). Statistically, 10 % of patients remain undiagnosed (Table 1).

The diagnostic search includes four steps (Fig. 1): identification of an additional sign, provisional hypothesis, additional diagnostic investigations, data interpretation, and comparison with the clinical case [4].

Currently, there isn't any universal diagnostic algorithm of FUO. During the past two decades, several diagnostic search designs were proposed; all of them have different structure and content. For instance, the algorithm by Roth A. and Basello G. (Fig. 2), which was presented in 2003, is more structured, more branched; unlike other variants, it provides for separate sets of examinations depending on the estimated ICD code. According to the algorithm proposed by Varghese et al. [6] in 2010, the first step includes a general medical examination, which is available in a majority of medical institutions; if no cause is found, then the second step follows, which is hi-tech examinations. Despite differences, these algorithms follow the principle of accessibility, stage-by-stage approach and cost-effectiveness. However, all algorithms are based on the personal experience of their authors and are not evidence-based.

During the diagnostic search, it is recommended to use symptomatic therapy only, namely antipyretics. Antibacterial therapy is indicated only in severe intoxication, haemodynamic disorders, signs of DIC-syndrome, neutropenia, and positive procalcitonin test. If system connective tissue disorders are suspected, test therapy with glucocorticosteroids (GCS) can be initiated, with

Table 1. *Causes of fever of unknown origin (adapted from Wright WF, Auwaerter PG. Fever and Fever of Unknown Origin: Review, Recent Advances, and Lingering Dogma. Open Forum Infect Dis. 2020 May 2;7(5):ofaa132. doi: 10.1093/ofid/ofaa132. PMID: 32462043; PMCID: PMC7237822.) [3]*

Category	Common	Uncommon
Infectious diseases	Mycobacterium tuberculosis (mainly extrapulmonary), endocarditis, culture-negative Epstein-Barr virus infections, cytomegalovirus infections	Bartonellosis (mainly Bartonella henselae), brucellosis, occult abscesses, salmonellosis, urinary tract infections, acute HIV, Hepatitis A, B, and E, Human herpesvirus-6, Human herpesvirus-7, bone and joint infections
Neoplastic diseases	Lymphoma (Hodgkin and non-Hodgkin), leukemia, solid-organ tumors (renal cell carcinoma and melanoma)	Myelodysplastic syndrom, colonic adenocarcinoma, multiple myeloma, gastric carcinomas, mesothelioma, Castleman's disease
Inflammatory diseases	Adult-onset Still's disease, systemic lupus erythematosus, polymyalgia rheumatica, temporal arteritis, inflammatory bowel disease	Rheumatoid arthritis, polyarteritis nodosa, sarcoidosis, granulomatosis with polyangiitis, Kawasaki's disease
Returnes travelers	Malaria, Dengue virus	Pulmonary infection, urinary tract infectoins, hepatitis A,B, and E, rickettsial deseases, leptospirosis, schistosomiasis, gnathostomiasis, cysticercosis, typhoid, acute HIV, tuberculosis
Miscellaneous	Medication / drug fever, chronic pulmonary embolism, hyperthyroidism, hematoma	Subacute thyroiditis, hypoadrenalism, necrotizinf lymphadenitis, periodic fevers (genetic), hemophagocytic lymphohistiocytosis, factitious fever.

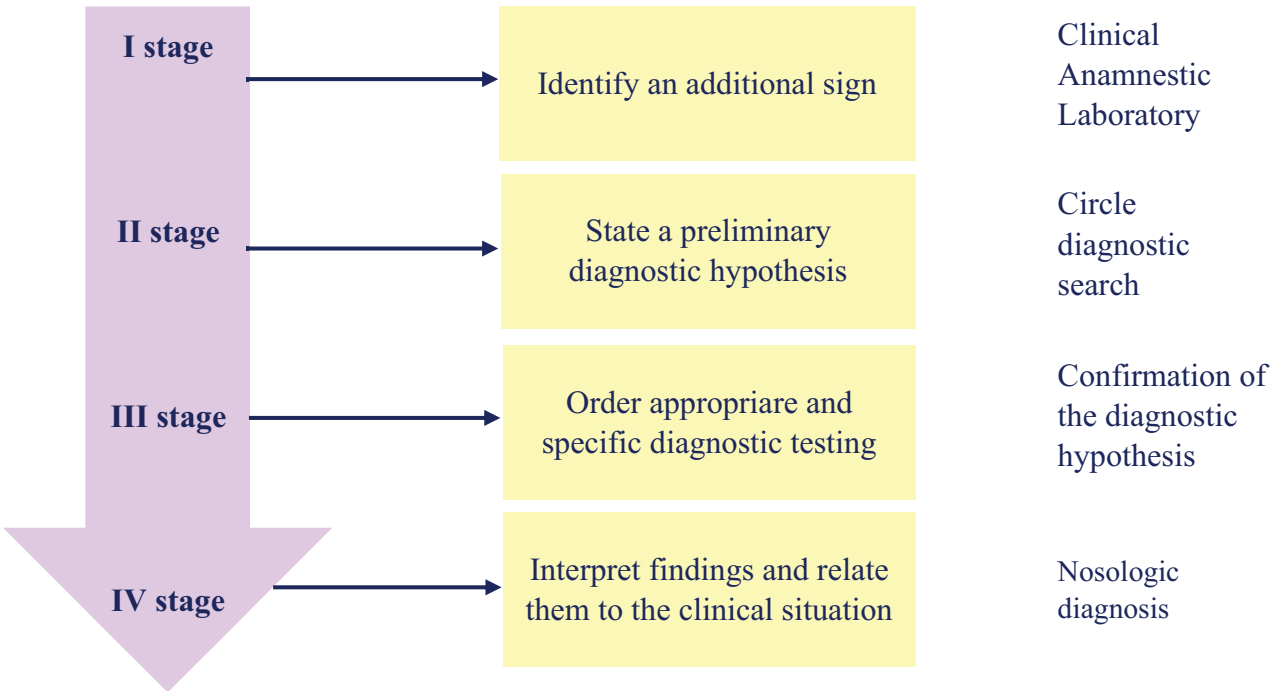


Figure 1. *Diagnostic search scheme of FUO (adapted from Dvoreckij L.I. Fever of unknown origin: an eternal clinical intrigue. Moscow, MEDpress-inform. 2019; 138 p. [In Russian]) [4]*

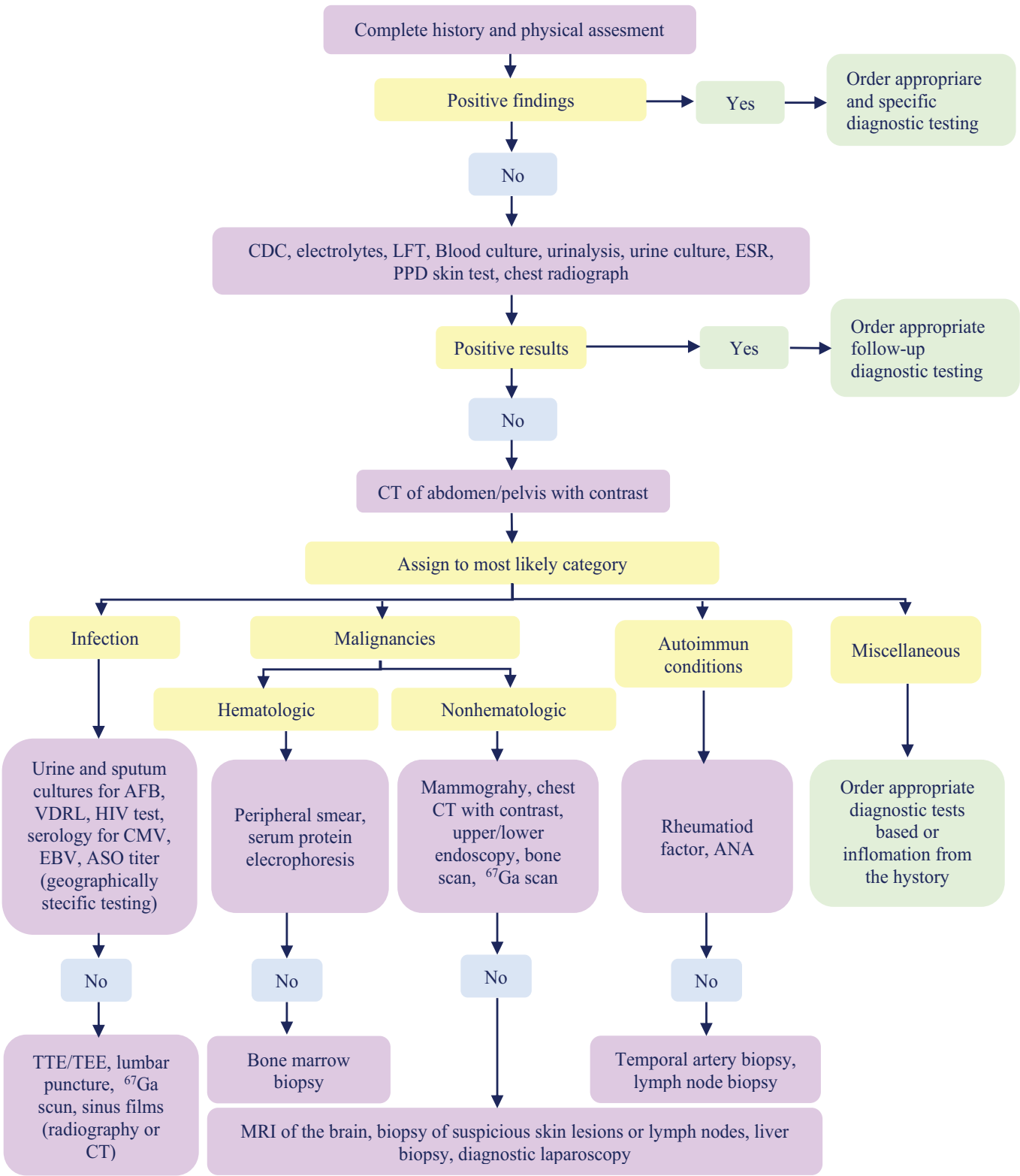


Figure 2. *Algorithm for the diagnosis of fever of unknown orogin Roth A., Basello G., 2003 (adapted from из Roth AR, Basello GM. Approach to the adult patient with fever of unknown origin. Am Fam Physician. 2003 Dec 1; 68(11): 2223-8. PMID: 14677667) [5]*

Note: CBC — complete blood count; LFT — liver function test; ESR — erythrocyte sedimentation rate; PPD — purified protein derivative; CT — computed tomography; AFB — acis-fast bacilli; HIV — human immunodeficiency virus; CMV — cytomegalovirus; EBV — Epstein-Barr virus; ASO — antistreptolysin-O antibodies; TTE — transthoracic echocardiography; TTE — transesophageal echocardiography; MRI — magnetic resonance imaging

efficiency assessment in 48–72 hours; if the therapy is inefficient, GCS should be discontinued.

If the cause of FUO is still unknown despite a comprehensive examination, case follow-up and laboratory monitoring are recommended, provided the patient is stable.

CASE STUDY

Patient M., 53 years old. On 17 April, she was admitted to the Department of Internal Medicine at the hospital of the Central Union of Consumer Cooperatives of the Russian Federation. The patient was complaining of a fever of 37.2–37.5 ˚C rising to 39.0 ˚C every 4–5 days for 1.5 months; pain on the left side of her face, increased fatigue, weakness, atony, apathy, irritability, poor concentration and attentiveness.

Medical history. The patient considers herself ill for four months, when psychoemotional stress caused exacerbation of recurrent neuritis of her left fifth cranial nerve, a condition, which the patient has had for the last five years, with annual recurrences; the condition is managed with pregabalin. The present episode of exacerbation manifests with headaches and pain on the left side of her face; the patient took pregabalin 600 mg and acyclovir, with no effect.

Early in February, the pain spread to the left temporal region and left eye area (Table 2).

Late in February, the patient had a high fever (39.5–39.9 ˚C) for three days; then it was a moderate fever (38.0–38.9 ˚C) for two weeks. Later, the patient had a subfebrile fever (37.2–37.5 ˚C) for 1.5 month, with rises in the body temperatures to 39.0 ˚C every 4–5 days (Fig. 3).

Over a period of two months, the patient repeatedly sought medical help. Outpatient examinations: ultrasound examination of neck, supraclavicular, subclavicular, axillary, and groin lymph nodes; paranasal sinus X-ray; consultation by a dentist — no pathologies.

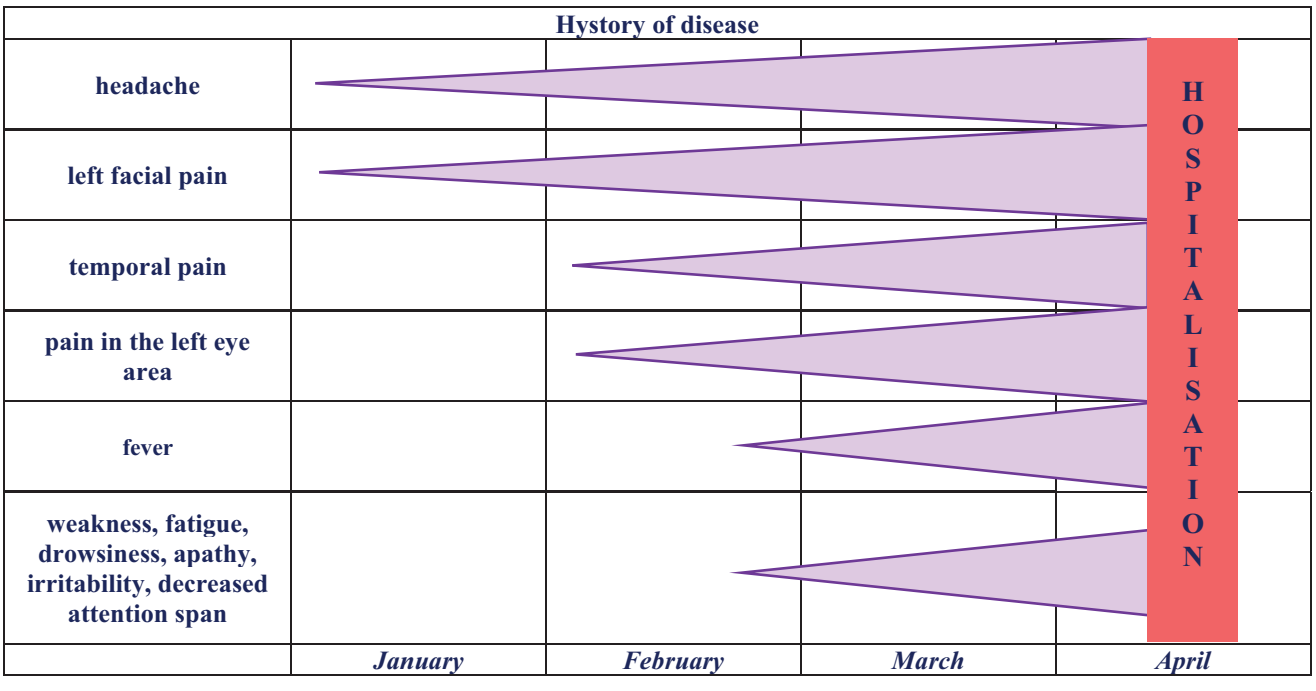
22 March: ultrasound examination of the thyroid gland, salivary glands, neck and submandibular lymph nodes. Echo signs of palpable abnormalities of the thyroid gland (13x10x7 mm, 15x13x9 mm, 12x10x9 mm) Thi-RADS 3–4 and diffuse changes in the right thyroid lobe, hyperplasia of the right paratracheal lymph node (6x5x4 mm) and moderate hyperplasia of two right submandibular lymph nodes (12x11x8 mm, 20x18x8 mm).

23 March: complete blood count — unremarkable; elevated ESR up to 38 mm/h; CRP (hsCRP) — up to 7.1 mg/L, TTH: 1.55 IU/L (normal range: 0.4–4.0 IU/L).

Biopsy of thyroid gland lumps: areas of colloid goitre with proliferated thyroid epithelial cells (Bethesda Category II — benign).

Past history. Type 2 diabetes mellitus from 2013; continuously takes insulin glargine 14 units once daily, metformin 1,000 mg twice daily. Recurrent neuritis of the left fifth cranial nerve from 2017. Positive family history for type 2 diabetes mellitus on her mother's side; her mother is followed-up to thyroid nodule. No bad habits. No history of allergies. Continuously takes atenolol 25 mg. The patient denies any trips outside the Moscow Region during the last six months. Any contact with contagious patients: denies. Any contact with animals, rodents, birds, animal raw materials: denies.

Table 2. *Dynamics of clinical symptoms*



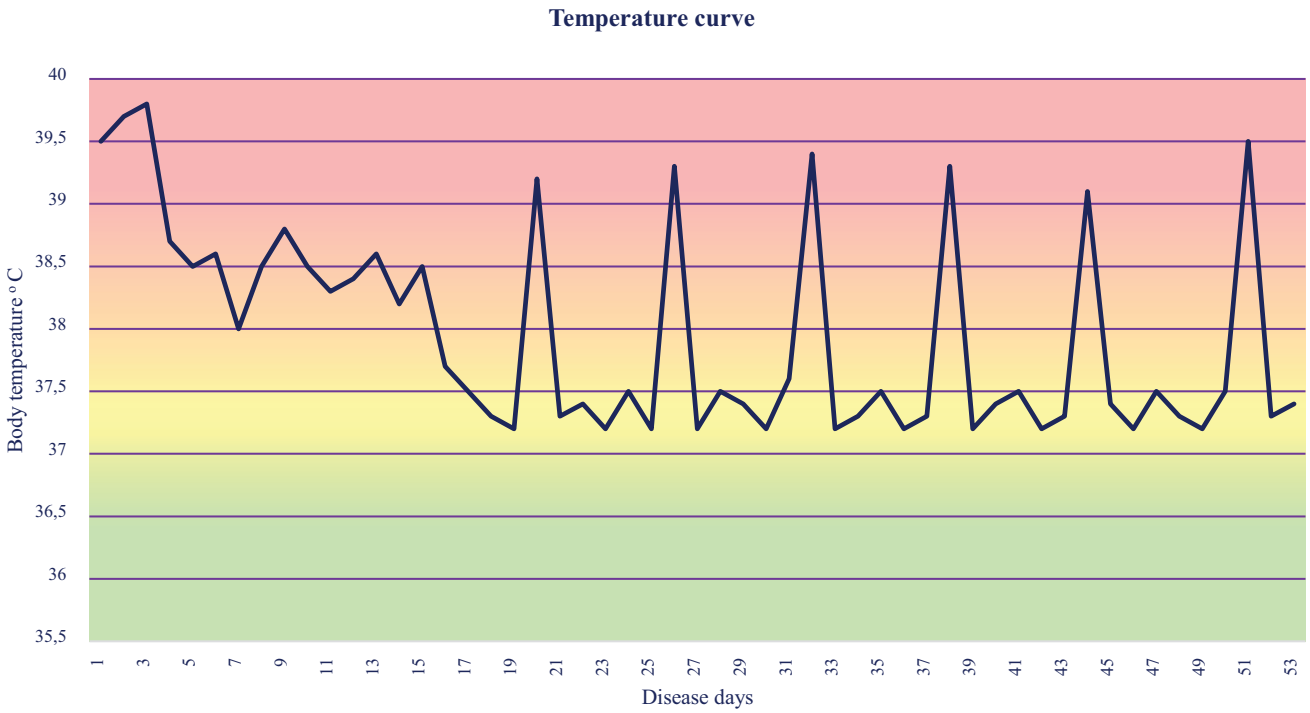


Figure 3. *Dynamics of the patient's body temperature outside the hospital*

Initial examination results dated 17 April: moderately severe condition; body temperature: 37.5 ° C. The oropharynx is not hyperaemic. Palpable enlarged submandibular lymph nodes on the left side. Respiratory rate: 19/min, vesicular respiration, without rales, SpO2: 98 %. Clear, rhythmic heart tones without any murmur; HR: 105 bpm; BP: 130/80 mm Hg; the thyroid gland is not enlarged, slightly painful. The patient is lucid, sensible, cooperative, emotionally labile. Other organs and systems: no abnormal changes.

Medical history and physical examination did not reveal any additional diagnostic sign. Examinations of the first-line diagnostic search: general clinical examinations, taking into account available outpatient examination and tests.

ECG dated 17 April: regular sinus rhythm. HR: 109 bpm. Sinus tachycardia. Horizontal CEA (cardiac electrical axis).

Complete blood count dated 17 April: HB — 112 g/L, EBC — 3.98 mln/μL, platelets — 372 ths/μL, WBC — 7.88 ths/μL, NEU — 60.3 % (4.75 ths/μL), LYMPH — 29.2 % (2.30 ths/μL), MONO — 7.7 % (0.61 ths/μL), EOS — 2.3 % (0.18 ths/μL), BAS — 0.5 % (0.04 ths/μL), HCT — 33.9 %, ESR — 105 mm/h.

Blood biochemistry dated 17 April: ALT — 10 U/L, AST — 10 U/L, albumin — 40 g/L, glucose — 7.7 mmol/L, creatinine — 64 μmol/L, urea — 5.7 mmol/L, total protein — 72 g/L, hsCRP — 69.8 mg/L, glycated Hb — 8.7 %, calcitonin — 1.8 pg/mL.

Urinalysis, ultrasound examination of abdomen, kidneys, pelvis, EcoCG: no abnormal changes.

At this stage, no clinically significant changes were observed, which would help to identify the key sign It was concluded that chest, abdominal, retroperitoneal and pelvic CT (with IV contrast) was required. The examination did not identify any meaningful pathologies of the chest, abdomen, or pelvis. However, structure inhomogeneity and contrast accumulation by thyroid parenchyma were reported.

Given the available information, changes in the thyroid gland revealed by the biopsy (taking into account normal hormone levels) were interpreted as signs of multinodal colloid goitre.

At this stage, examination results did not make it possible to choose a certain group of diseases. Initial examinations for all categories of diseases have been performed.

Blood test for autoimmune markers dated 18 April: rheumatoid factor — < 20.0 IU/mL, antinuclear antibodies (ANA IIFT, HEp-2) — <1:160 titer.

Blood test for infections dated 18 April: EBV virus DNA — negative; type 6 herpes simplex virus — negative.

In order to rule out a septic process, blood test for procalcitonin (0.03 ng/mL) and blood culture for sterility (no microflora growth) were performed.

Examinations: paranasal sinus CT, mammography, esophagogastroduodenoscopy, fibrocolonoscopy — no clinically significant changes.

Repeated blood tests dated 24 April showed the following abnormalities: Hb — 109 g/L, HCT — 32.9 %, ESR — 99 mm/h, albumin — 34.5 g/L, CRP — 60.4 mg/L.

Since there was no key sign, and CT changes in the thyroid gland were reported, TTH levels were measured: < 0.0083 IU/L (23 March: 1.55 IU/L).

The key sign was identified — thyrotoxicosis, which was not observed one month earlier. Follow-up examinations of the thyroid gland were performed.

Blood test dated 25 April: TTH receptor antibodies — 1.0 IU/L (negative); free T3 — 5.5 pmol/L (3.0–5.6 pmol/L); free T4 — 33.05 pmol/L (9.00-19.05 pmol/L).

Thyroid ultrasound (Fig. 4) as compared to 22 March demonstrated an enlarged thyroid gland: right lobe — 19×18×47 mm→23×20×55 mm, left lobe — 18×16×43 mm→18×18×50 mm, isthmus — 3 mm→5 mm, volume: 12 cm^3→20.1 cm^3. Parenchyma: mixed echogenicity, marked diffuse heterogeneity,

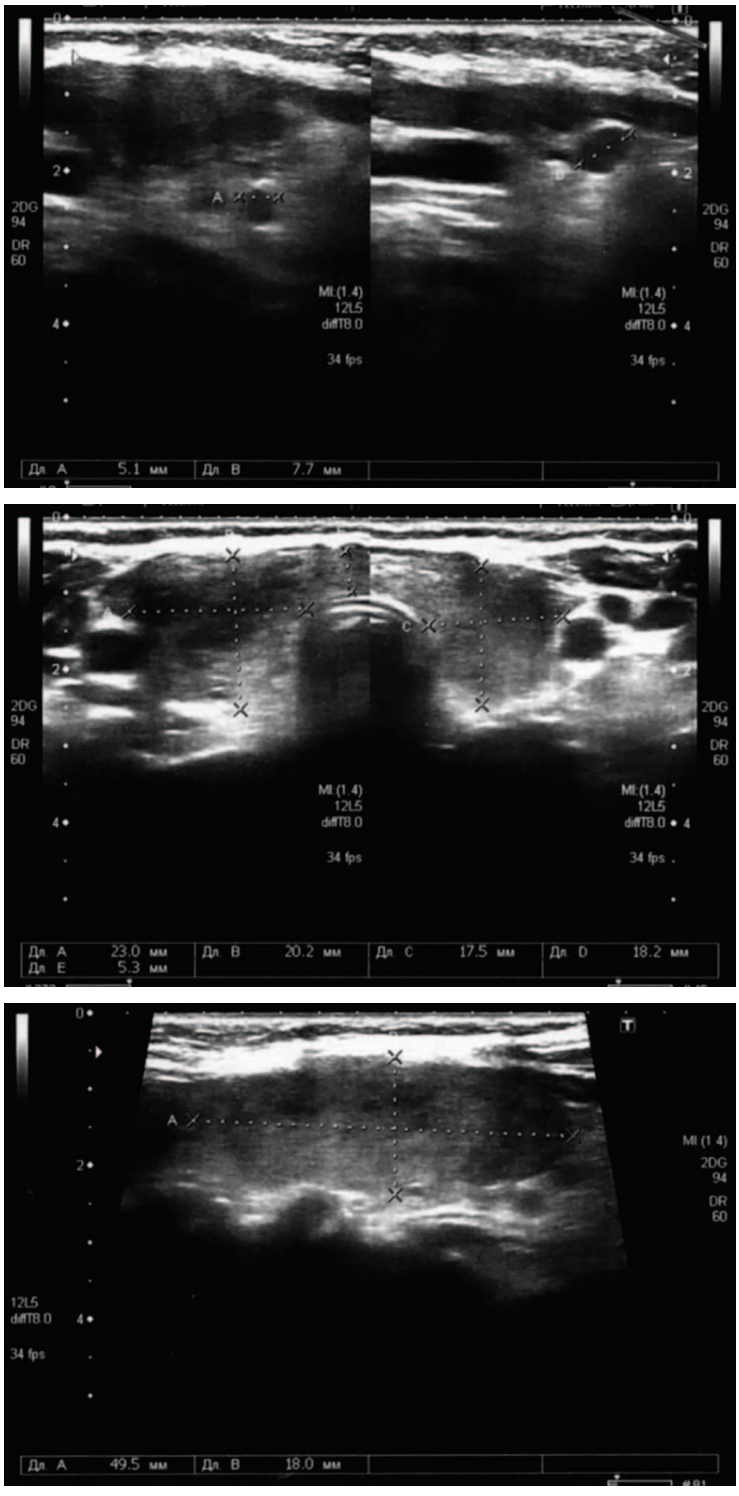


Figure 4. *Thyroid ultrasound 25.04*

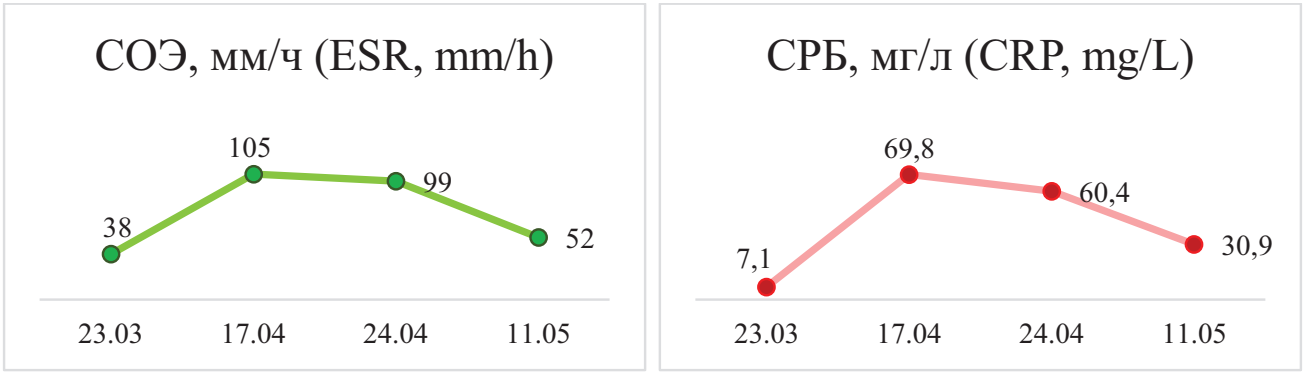


Figure 5. *Dinamics ESR and CRP over the observation period*

more in the right lobe, with large areas of decreased echogenicity in the whole lobe. The lower body of the right lobe: the above-mentioned hypoechoic node with even, unclear edges cannot be differentiated due to the overall lobe heterogeneity. The above-mentioned areas of reduced echogenicity along the posterior surface with uneven, unclear edges and without enhanced blood flow, which were interpreted as Thi-RADS 4, have now amalgamated with the large areas. In the central segment there is an isoechoic node with even, unclear edges, 15×13×9 mm.

The patient was consulted by an endocrinologist; the following diagnosis was made on the basis of laboratory and instrumental test results: severe subacute thyroiditis.

Laboratory tests showed thyrotoxicosis syndrome, pain syndrome, accelerated ESR syndrome, typical ultrasound changes in the thyroid gland.

According to the clinical recommendations for the management of acute and chronic thyroiditis [7], the patient had a prednisolone challenge test, i.e. test therapy: prednisolone 20 mg once daily. On day 2 of therapy, the body temperature normalised; on day 3, weakness, apathy, irritability resolved; and on day 4, the pain syndrome resolved completely.

An analysis of the clinical, laboratory and instrumental data as well as medical history confirm the diagnosis of severe subacute thyroiditis:

- Palpatory tenderness of the thyroid gland
- Fever
- Thyrotoxicosis syndrome
- Accelerated ESR syndrome without leukocytosis
- Enlarged thyroid gland, areas of decreased echogenicity, migration of these areas on ultrasound
- Positive prednisolone challenge test.

Final diagnosis: Severe subacute thyroiditis. Type 2 diabetes mellitus, target HbA1c of less than 7.0 % has not been achieved. Mild normocytic, normochromic anaemia.

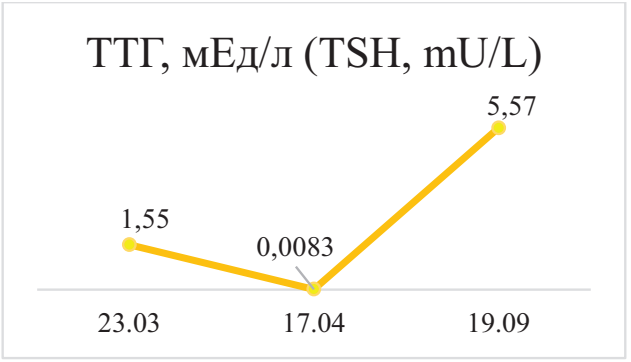


Figure 6. *Dynamics of thyroid-stimulating hormone levels during the observation period*

The patient was discharged with improvements and was given the following recommendations:

- Prednisolone 20 mg once daily, weekly follow-up complete blood counts (including ESR); once ESR has normalised, prednisolone dose should be reduced by 2.5 mg (1/2 tablet) every week until complete withdrawal
- Atenolol 25 mg once daily (in the morning)
- Insulin glargine 14 units once daily
- Metformin 1,000 mg twice daily (in the morning and before bed)
- Empagliflozin 10 mg once daily
- Omeprazole 20 mg twice daily.

1.5 months later, the patient started reducing prednisolone dose, and by the end of August, she withdrew from it completely. According to laboratory blood tests, in mid-September the patient had asymptomatic hypothyroidism, which corresponds to the hypothyroid phase of destructive (subacute) thyroiditis: TTH — 5.57 IU/L (0.4–4.0 IU/L), free T3 — 5.14 pmol/L (3.0–5.6 pmol/L), free T4 — 10.81 pmol/L (9.0–19.05 pmol/L).

Discussion

The peculiarities of this clinical case are the rare incidence of this pathology, lack of unified management recommendations and long diagnostic search due to uncharacteristic clinical manifestations.

There is literature evidence of FUO caused by subacute thyroiditis, where local symptoms and signs of impaired thyroid function are not primary aspects. In FUO, pain syndrome can be mild or can be absent; in some cases, patients recalled short-term pain or discomfort in the neck area, which is not typical of the traditional course of subacute thyroiditis.

In this case, pain syndrome has an atypical location.

Symptoms of thyrotoxicosis were unclear, which can be a result of beta-blockers inhibiting manifestation of thyrotoxicosis (non-selective beta-blockers have a more pronounced effect).

Also, the diagnostic process was challenging due to the available outpatient data of thyroid data examinations and absence of any clinical signs for a follow-up examination. According to the clinical recommendations on thyroid disorders, TTH levels are monitored every eight to 12 weeks. An examination performed in March showed euthyroid state; however, the thyrotoxic phase of destructive thyroiditis set in within one month. Ultrasound results made it possible to monitor changes in the thyroid gland, including signs typical of subacute thyroiditis (migration of hypoechoic cloud-shaped areas).

Of note, available data of thyroid gland examinations hindered diagnostic search; pain syndrome and initial examination results were misinterpreted. It is likely that outpatient blood tests and thyroid ultrasound were performed at the early stage of disease, i.e. at the beginning of destructive thyrotoxicosis (Fig. 7), when the thyroid function had not yet responded to the existing inflammation and starting thyrocyte destruction. Also, ultrasound results were not pathognomonic for subacute thyroiditis; and they could be interpreted only during the follow-up (migration of hypoechoic cloud-shaped areas).

In this case, differential diagnosis with giant cell arteritis (GCA) was required. The patient had typical pain location. However, upon examination the patient did not present with typical changes in her temporal areas (temporal artery bulging and a clearer contour, palpatory tenderness of skin of the head and temporal region); also, there were no symptoms of muscle involvement (myodynia, alternating mandibular claudication), etc.

A positive effect of GCS is typical for both diseases; however, in GCA, higher doses of GCS are used for approximately 24 months; any attempts to reduce the dose or discontinue GCS can cause a relapse. In this case, 1.5 months after therapy initiation, laboratory values normalised, and two months later, the therapy was discontinued completely. The patient's condition did not deteriorate, while thyroid hormone levels corresponded to subclinical hypothyroidism, which correlates with stage 3 subacute thyroiditis (transient thyroiditis).

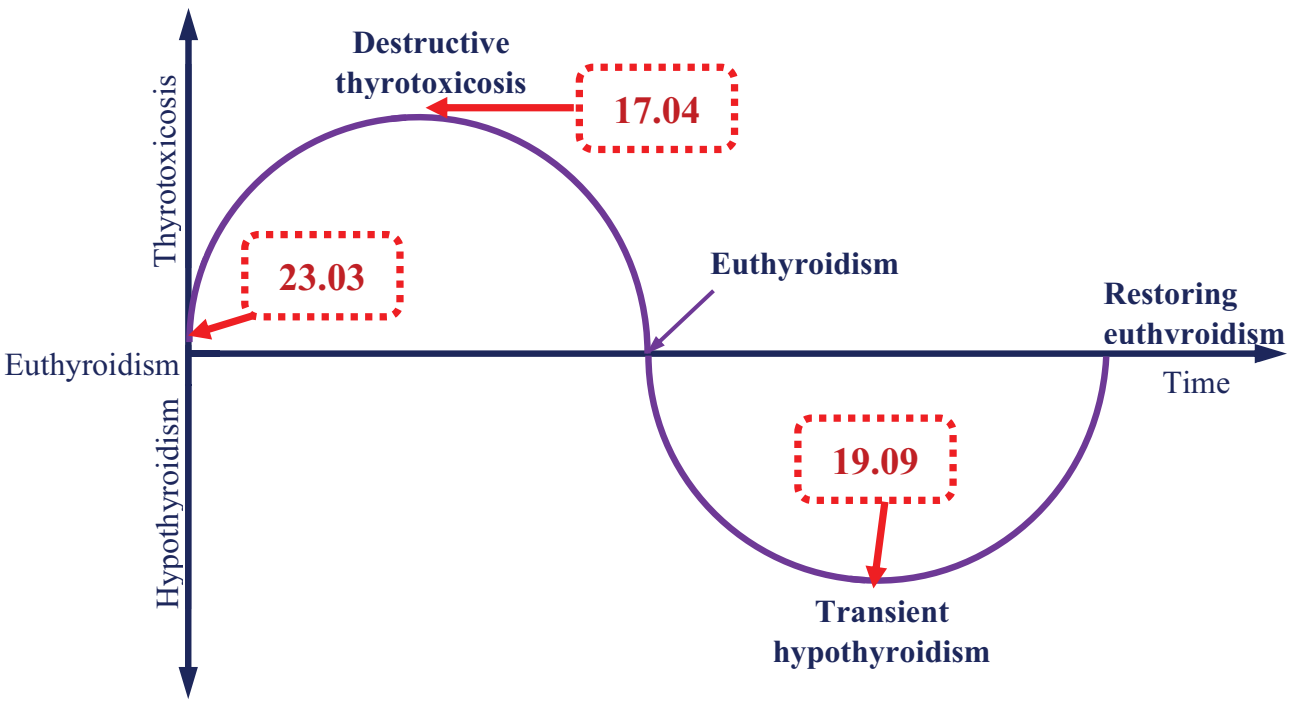


Figure 7. *Stages of subacute thyroiditis*

Conclusion

This clinical case demonstrates challenges of management of patients with fever of unknown origin. Versatile causes, belonging to various areas of medicine, usually an atypical clinical presentation of the disease disguised by FUO, poor awareness among healthcare providers of the causes (including rare cases, such as subacute thyroiditis) and diagnosis of this condition, lack of clinical recommendations on the management of such patients, hinder diagnostic search and extend the time needed to make a diagnosis.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Фомина Е.И.: ведение пациента, разработка дизайна публикации, написание текста рукописи, обзор публикаций по теме статьи, утверждение окончательного варианта, принятие ответственности за все аспекты работы, целостность всех частей статьи и ее окончательный вариант, взаимодействие с редакцией в процессе подготовки публикации и печати

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Адашева Т.В.: научное руководство, разработка концепции, сбор данных и обработка материала, подготовка и редактирование текста, утверждение окончательного варианта

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Fomina E.I.: patient management, development of the publication design, writing the manuscript text, review of publications on the topic of the article, approval of the final version, taking responsibility for all aspects of the work, the integrity of all parts of the article and its final version, interaction with the editorial board during the preparation of publication and printing

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